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13. ABSTRACT *(Maximum 200*

This career development award is allowing me to increase my expertise in the area of hormones, hormonally-related factors and risk of breast cancer. I proposed to prospectively assess plasma hormone levels, alcohol use and body fat distribution in relation to breast cancer risk. In year one of the grant, I received laboratory results for 155 breast cancer cases and 310 matched controls from a case-control study nested within the prospective Nurses' Health Study. Several primary estrogens (estradiol [both free and bound fractions], estrone, estrone sulfate) and androgens (testosterone, androstenedione, DHEA, DHEAS) and prolactin were assayed. Statistical analyses of these data are ongoing and a manuscript is being prepared. Additionally, I have begun the analyses of alcohol intake and risk of breast cancer.

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Susan C. Faux 7/30/97
PI - Signature Date

Table of Contents

I. Introduction

My long-term career objective is to help resolve outstanding questions concerning endogenous and exogenous hormones and breast cancer. Specifically, I wish to address the relationships between specific postmenopausal and premenopausal hormone levels and breast cancer risk. Also, I wish to examine which breast cancer risk factors operate through a hormonal mechanism, how these factors interact and how they can be modified. The funded analyses will not only give me invaluable experience in the area of hormones and breast cancer, thus providing the background necessary to conduct independent research, but will contribute significantly towards current knowledge in this area.

I proposed addressing the following hypotheses:

1. Plasma sex hormone levels and risk of breast cancer among postmenopausal women:

a. **Estrogens:** Total estradiol, percent free estradiol, percent bioavailable estradiol (the sum of percent free and percent albumin-bound estradiol), estrone, and estrone sulfate each increase risk of breast cancer.

b. **Androgens:** Androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) each increase breast cancer risk.

c. **Prolactin** increases risk of breast cancer.

2. Alcohol intake and breast cancer risk.

a. Moderate alcohol consumption increases the risk of breast cancer and this risk varies by when in life exposure occurs.

b. This increased risk of breast cancer varies by levels of other risk factors including age, menopausal status, body mass index and family history.

3. Body fat distribution (as assessed by the waist-to-hip ratio) and breast cancer risk.

a. Higher waist-to-hip ratios increase breast cancer risk.

b. This increase in risk varies by level of other breast cancer risk factors including age, menopausal status, body mass index, and family history.

As part of my Career Development Award, I also proposed attending several Endocrinology courses at Harvard Medical School.

Background and Significance.

A. Plasma Hormones and Breast Cancer. The epidemiology of breast cancer suggests an etiologic role for endogenous sex hormones: reproductive factors including age at first birth, parity, age at menarche and menopause, and possibly lactation influence breast cancer risk (1). Hormonal manipulations such as anti-estrogens and adrenal suppression have been useful in the treatment of breast cancer. Furthermore, estrogens and prolactin promote mammary tumors in animals (2).

The relation between plasma estrogens and the risk of breast cancer has received the greatest attention. Estradiol, generally considered the most biologically active endogenous estrogen, circulates in blood bound either to sex hormone binding globulin (SHBG) or albumin, or unbound

("free" estradiol). Data from several previous case-control studies (3,4,5,6) but not others (7,8,9) suggest that high levels of estradiol increase the risk of breast cancer. Higher free estradiol levels among cases were observed prospectively (10) and in several case-control studies (4,7,9,11,12) but not in others (8,13,14,15). Recently, in the largest prospective analysis to date, (130 cases and 260 controls) Toniolo et al. (16) reported a significant 2 to 4 fold increased risk of breast cancer among women in the top versus bottom quartile of plasma estradiol, % free estradiol and % bioavailable estradiol levels. Estrone is the predominant estrogen and the source of much of the circulating estradiol in postmenopausal women. Higher estrone levels were significantly associated with increased breast cancer risk in the study by Toniolo (16) and in one of the larger case-control studies (17); a nonsignificant positive association was noted in several other case-control studies (7,6). No association was found in other studies (8,13,14,18,19).

In a prospective analysis, postmenopausal women who developed breast cancer had a nonsignificant elevation in plasma testosterone and androstenedione compared to controls (18); in a second analysis with 42 mixed incident and prevalent cases no association was noted (13). In a prospective analysis, Gordon et al (20) reported that, relative to controls, cases had a significant 33% higher level of plasma dehydroepiandrosterone (DHEA) and a nonsignificant 16% increase in DHEAS. In several case-control studies, strong positive associations have been observed between levels of plasma testosterone and breast cancer risk among postmenopausal women (17,21,22,23). The biologic mechanism behind an association with androgen levels is less clear but might be related to their conversion to estrogens.

Strong evidence links prolactin to the induction and progression of mammary carcinoma in the rat and mouse (24). In addition, prolonged reductions in prolactin occur after first pregnancy (25) and prolactin levels are higher in women at increased risk of breast cancer due to first pregnancy over the age of 35 years (26), nulliparity (27), and family history (28). In postmenopausal women, prolactin was associated with increased risk of breast cancer in the only prospective study (29) as well as several (30,31), but not all (6,24), case-control studies.

B. Alcohol Intake and Breast Cancer Risk. Epidemiologic data have continued to accumulate indicating that alcohol intake is associated with increased risk of breast cancer (32). Results from at least 35 case-control studies and 12 follow-up studies have been reported. All but six case-control studies observed a positive association, as did nine of 12 follow-up studies. Two of the follow-up studies were equivocal, and one small study reported an inverse association. Longnecker et al. (33) conducted a meta-analysis and found a dose-response relation in both the case-control and cohort data, though the association was stronger in prospective studies; they concluded that the evidence strongly supported an association between alcohol consumption and risk of breast cancer. In a more recent, updated meta-analysis (unpublished) Longnecker again concluded that strong evidence supported such a relation.

Results of several studies suggest that alcohol consumption at an early age has a particularly strong relation with subsequent risk of breast cancer with relative risks ranging from 1.5 to 2.5 (34,35,36). However, this finding has not been observed in other studies (37,38,39). Of particular interest is the observation of Harvey et al. (36) who studied the influence of alcohol use at different ages; the positive association was entirely attributable to alcohol use before the age of 30 years. However, just 15 cases drank before age 30 and later stopped, so that the distinction between those who continued and those who stopped is unstable. Similarly, Hiatt et al (35) observed an

increase in risk among past drinkers compared with women who never drank (RR=2.2), although the age at quitting drinking was unspecified. This relation with drinking at younger ages, however, is consistent with other data, such as studies of radiation exposure, indicating that the breast is particularly susceptible during early adult life to factors that influence cancer risk (and perhaps specifically before a first pregnancy that results in terminal differentiation of the breast tissue).

In several studies the increased risk due to alcohol use was assessed within strata of other factors including age, menopausal status, body mass index, postmenopausal hormone use, and family history. Evidence of effect modification was reported in some studies (e.g., greater risk in younger (40,41) and thinner (37,41,42) women) but not in other studies (by age: 38,39; by BMI: 42,38). It is not obvious why these findings are so inconsistent, however, the comparisons often were based on small numbers of cases and were conducted in case-control studies where selection or recall bias can not be ruled out. The identification of specific subgroups of alcohol users with a particularly increased risk of breast cancer would be helpful to women in making personal decisions regarding their alcohol consumption and would assist in further delineating high risk groups for increased screening.

C. Body Fat Distribution and Breast Cancer Risk. Abdominal obesity (as measured by the waist-to-hip ratio), independent of body mass, has been hypothesized to increase risk of breast cancer, perhaps through an increase in either total or bioavailable steroid hormone levels (43,44). To date, few studies have examined this hypothesis. In recent prospective (45,46) and case-control studies (47,48), a positive association has been reported (RR=1.4-1.8). In a third prospective study (49), no association was found although this study was small with only 23 cases. In the Iowa Women's cohort, the association between waist-to-hip ratio and breast cancer risk was strongest in older women with a higher body mass index (46) and among women with a family history of breast cancer (50). Bruning et al (49) reported that waist-to-hip ratio, rather than body mass index, increased breast cancer risk in postmenopausal women, while in premenopausal women the opposite was true. To my knowledge, the interrelationship of these variables has not been assessed in other studies. These issues will not be addressed until year 3 of this grant.

Previous Work

A. The Nurses' Health Study (NHS) Cohort.

In 1976, 121,700 female U.S. registered nurses between the ages of 30 and 55 years completed the initial NHS questionnaire forming the NHS cohort. The population is predominantly white, reflecting the ethnic background of women entering nursing in the U.S. in the 1950's and 1960's. The cohort is approximately 1.2% African-American, 0.6% Hispanic, 0.8% Asian, 17% Southern European or Mediterranean, 7% Scandinavian, 60% other Caucasion, and 4% other ancestry. The cohort has been followed by mailed questionnaires sent every two years; nonrespondants to questionnaires are telephoned. Follow-up, calculated as a percentage of total possible follow-up time, was over 92% in 1990.

Since the study began in 1976, extensive information has been collected on exposures that will be important covariates in the proposed analyses. These include height, weight, age at menarche and menopause, age at first birth, parity, lactation, oral contraceptive and postmenopausal hormone

use, smoking history, physical activity, history of benign breast disease, family history of breast cancer and dietary intake. In 1980, a 61-item dietary questionnaire was sent to participants; this questionnaire has been studied intensively for reproducibility and validity (51,52). More extensive dietary questionnaires were included in the 1984, 1986, and 1990 follow-up; over 80 nutritional parameters are measured.

Nonfatal breast cancer cases are reported on the questionnaire and by telephone interview. These women are asked to grant us permission to review their medical records to confirm the self-reported diagnosis and to further classify the cancer by histologic type, size, receptor and nodal status. Approximately 99% of reported breast cancer diagnoses are confirmed upon medical record review. To identify cases among non-respondents, the National Death Index is searched and death certificates obtained. Incident cancers identified from death certificates require medical records to be classified as confirmed cancers.

B. Biochemical Markers in the Nurses' Health Study

In 1989 and 1990, we obtained blood samples from 32,826 NHS participants (NIH CA 49449; Frank Speizer, PI). Each woman was sent a blood collection kit which contained all the needed instructions and supplies to have blood drawn and mailed back to our laboratory. We enclosed a questionnaire which requested information on the date and time the sample was drawn, time since last meal, current menopausal status, and recent hormone use. Each participant made arrangements for the blood sample to be drawn, generally by her physician, a colleague, or a local laboratory. The blood samples were returned to our laboratory via overnight courier; 97% of the samples arrived within 26 hours of being drawn. Of over 64,000 blood tubes received, only 75 tubes were broken in transit.

Upon arrival in our laboratory, the blood samples were centrifuged and blood components aliquotted into plasma, white blood cell, and red blood cell components. Cryotubes are stored in 17 liquid nitrogen freezers. All nitrogen freezers are connected to an electronic alarm system and are monitored 24 hours a day. For added security, each participant's sample is stored in 3 different freezers.

C. Previous Research Experience.

I graduated with a B.S. in nursing in 1979 and worked as a nurse for 6 years. In 1992, I graduated from the Harvard School of Public Health with a doctoral degree in epidemiology. My doctoral thesis addressed risk factors for senile cataract, in particular dietary intake (53), smoking (54), and aspirin use (55). In 1988, I organized and directed several studies that lay the groundwork for the large NHS blood collection effort, including an assessment of the validity of our blood collection methods with a focus on micronutrients and hormones (56). I have been the Project Director of the Biochemical Marker Study (CA 49449) since it was funded in 1989; in this capacity, I planned, organized and directed the collection and archiving of the 32,825 blood samples. My original focus in this study was to assess nutritional biomarkers of cataract risk.

In 1992-93, I completed a post-doctoral fellowship at the Channing Laboratory during which time I evaluated the stability of a number of biomarkers during transport (66), assessed laboratory reproducibility of plasma hormone measurements (57) and the stability of hormone levels in postmenopausal women. During this time, I also assessed the relationship between both oral contraceptives (58,59) and tubal ligation (60) and ovarian cancer.

II. Body of Report

In year 1, I began the analyses of plasma hormone levels and risk of breast cancer, and have just begun the alcohol and breast cancer analyses. Originally I planned to conduct many of the analyses of alcohol and breast cancer in year one. However, the plasma hormone values were ready earlier than I expected, and by delaying the start of the alcohol analyses (and allowing our study staff to complete another two year cycle of disease follow-up), I now have over 600 more breast cancer cases available for the analysis - a substantial benefit. Thus most of my effort this year was directed towards the hormone (rather than alcohol) analyses. Additionally, I attended a course on endocrinology at Harvard Medical School. Each of these activities is outlined below.

A. Study of Plasma Hormones and Breast Cancer Risk.

1. Identification and preparation of specimens for analysis. All documented cases of incident breast cancer occuring from after the blood collection up to June 1, 1994 serve as cases for this analysis. For each breast cancer case with a blood sample, two control subjects were selected at random from among individuals of the same age ($\pm$1 yr) and who gave blood at the same time ($\pm$1 month) who were at risk of disease at the time the case occurred (61). Women with a prior history of cancer were excluded from these analyses. I also matched by menopausal status and by time of day the blood sample was drawn. There were 155 cases and 310 controls in total. Samples were pulled from the freezers, aliquotted and sent to the laboratories for analysis.

2. Measurement of Hormone Levels. With the exception of prolactin, all hormone analyses were conducted at Nichols Laboratory, San Juan Capistrano, California. Prolactin was assayed at the laboratory of Dr. C. Longcope at the University of Massachusetts Medical Center. The samples were labelled by number only, and matched case-control pairs were handled identically and together, shipped in the same batch, and assayed in the same analytical run. The order within each case-control pair was determined at random. Aliquots from the pooled quality control specimens were analyzed periodically by each laboratory to monitor quality control. These aliquots were indistinguishable from the real specimens, and were interspersed among them without the knowledge of the laboratory personnel. All between-assay coefficients of variation were $\leq$15%.

3. Data Analysis and Results. After log transforming the values to improve normality, mean levels among cases and controls were compared by t-tests. No significant differences were noted for percent free estradiol, percent bioavailable estradiol, androstenedione, and DHEA. Small, not quite significant differences (with cases higher than controls) were noted for estradiol and testosterone. Cases had significantly higher levels than controls for estrone, estrone sulfate, DHEAS and prolactin. Using conditional logistic regression, I also analyzed hormones and breast cancer using exposure levels divided into quartiles using the distribution of the controls. The table below shows these results.

Table 1. Relative risk (RR) of breast cancer (and 95% confidence interval) by quartile of plasma hormone level.

Plasma Hormone	Quartile 1	2	3	4	95% CI Quartile 4 versus 1
Estrone (pg/ml)	≤21	22-28	29-38	39+	
RR	1.0*	1.75	1.97	2.16	1.18-3.99
Estradiol (pg/ml)	≤5	6-7	8-11	12+	
RR	1.0	1.12	1.09	1.73	1.00-2.99
% Free Estradiol	≤1.43	1.44-1.55	1.56-1.70	1.71+	
RR	1.0	0.70	0.98	1.23	0.13-5.01
% Bioavailable Estradiol	≤17.38	17.39-23.0	23.1-31.38	31.39+	
RR	1.0	0.84	0.78	1.19	0.70-2.02
Androstenedione (ng/dl)	<41	41-57	58-77	78+	
RR	1.0	1.33	1.74	1.50	0.58-4.66
DHEA ng/dl	≤131	131.1-205	205.1-284	284.1+	
RR	1.0	0.88	0.90	1.25	0.71-2.21
DHEAS ng/dl	≤48	49-78.5	79-124	125+	
RR	1.0	2.15	1.68	2.10	1.12-3.91
Testosterone ng/dl	≤15	16-22	23-31	31+	
RR	1.0	1.12	1.10	1.34	0.74-2.44
Estrone sulfate pg/ml					
group 1	≤118	118.1-164	164.1-227	227.1+	
RR	1.0	0.82	0.85	1.85	0.67-5.06
group 2,3	≤141	141-205	205-299	299+	
RR	1.0	0.98	1.28	2.17	1.09-4.33
All groups combined but different cutpoints for group 1, 2, 3 (as above)					
RR	1.0	0.93	1.12	2.09	1.19-3.69

Because estrone sulfate levels varied substantially by batch (three different batches of samples were assayed at three different times), batch specific cut-points were used in the analyses. Overall, we observed positive associations between several of the hormones and breast cancer, particularly estrone, estrone sulfate and DHEAS.

The NHS questionnaires provide much useful data for control of possible confounding and for the assessment of possible effect modification in these analyses. I am currently assessing confounding by known and hypothesized breast cancer risk factors: parity, age at menarche and menopause, age at first birth, alcohol use, obesity (i.e., BMI or weight/height^2), lactation, history of benign breast disease, fat and fiber intake, and family history of breast cancer. Several of these risk factors may in fact be in the causal pathway and thus should not be adjusted for; this is being carefully evaluated.

Drs. Rosner and Willett have developed methods to correct relative risks and confidence intervals from logistic regression analyses, both in the case of one independent variable measured with error (62), and when multiple variables are measured with error (63). Both these methods take into account uncertainty in the estimation of measurement error. I am currently working with these investigators to apply their methods using the data on within-person variation from the subset of women who donated three blood samples over 4 years. These analyses will be completed within the next two months and a manuscript will be submitted for publication.

B. Analyses of Alcohol Use and Breast Cancer

This year the 1994 breast cancer data files were completed and cleaned. I am now starting the analyses of this association and will have preliminary results in the next month. The analyses will be completed in year two of the grant period. An outline of what I am doing is given below.

I will be making several primary sets of comparisons. First, I will assess the relationship between alcohol use as assessed in 1980 and subsequent breast cancer risk from 1980-1994 and this relation within categories of other risk factors (e.g., age, menopausal status). In addition, I will examine different types of alcoholic beverages separately and will update alcohol exposure using data from 1984 and 1986.

Second, using exposure data reported in 1988, I will examine the relationship between age at alcohol use (and amount of use) with breast cancer diagnosed 1988-1994. I will enter variables representing past use and current use in the same model to assess which is the most relevant exposure period. In addition, I will assess recent patterns of alcohol consumption (i.e., usual number of days/ week that alcohol is consumed, largest number of drinks consumed in a single day). I will also construct a variable which estimates "lifetime" alcohol dose using responses to the amount of alcohol consumed at different periods of life (ages 18-22, 25-30, 35-40, and as more recently reported on the multiple food frequency questionnaires). These analyses should help discern what aspect(s) of alcohol consumption is most associated with risk.

C. Training.

One of my objectives in applying for this CDA was to increase my knowledge in the area of endocrinology. To help meet that objective, I attended HT060 (described below) this year. Unfortunately, I did not find it sufficiently detailed in terms of reproductive endocrinology to meet my needs. Thus I currently plan to attend a specific course on reproductive endocrinology next spring (HT070 Human Reproductive Biology).

Endocrinology (HT060) "In this course students study physiology and pathophysiology of the human endocrine system. The format of the course includes both didactic lectures on the various glandular systems and presentations of clinical cases with relevent laboratory information. The cases serve to illustrate the pathophysiology of endocrine diseases."

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DEPARTMENT OF THE ARMY
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 29 May 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request for Change in Distribution Statements

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Grant DAMD17-96-1-6021. Request the limited distribution statements for Accession Documents Number ADB231829 and ADB239327 be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management